# Interaction of Familial and Hormonal Risk Factors for Breast Cancer[1]

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ABSTRACT—A case-control study, conducted among participants in the Breast Cancer Detection Demonstration Project, obtained detailed information on family history of breast cancer and other risk factors from 1,362 breast cancer patients and 1,250 control subjects. An affected first-degree relative was reported by 22.4% of the patients and 12.2% of the control subjects. This finding was associated with a twofold increased risk of breast cancer, although greater elevations in risk were seen in younger study subjects and in those reporting both an affected mother and a sister. Analysis of other risk factors showed that, compared to women without a family history of breast cancer, control subjects with a family history of breast cancer tended to have early or late menarche, were older at first childbirth, and were younger at oophorectomy. In addition, the effect of family history on breast cancer risk was modified by age at menarche, but not by age at first birth or type of menopause. These findings suggest that familial susceptibility to breast cancer may be mediated through hormonal factors that operate early in a woman's life. A synergistic relationship was also observed between family history of breast cancer and the occurrence of multiple biopsies for benign breast disease, although the mechanisms for this relationship remain to be elucidated.—JNCI 1982; 69:817–822.

The familial aggregation of breast cancer has been well established (*1–7*). However, apart from examining differential effects according to age at diagnosis and/or menopause status (*8–12*), few studies have assessed the interaction of familial susceptibility with other risk factors for breast cancer. Bain et al. (*13*) examined family history in relation to a variety of risk factors and found the effects most pronounced in women with younger ages at disease onset and in those who had menstruated for more than 35 years. However, this study included few older women and was not able to assess fully the effects of family history according to cessation of menstrual function. An understanding of how hormonally related factors interact with familial occurrence is of particular interest, given the strong relationship of ovarian function to breast cancer risk (*14*) and laboratory evidence suggesting that familial predisposition to breast cancer is mediated through hormonal mechanisms (*15–18*).

With the use of data collected from participants in the BCDDP, we had the opportunity to evaluate family history of breast cancer as a risk indicator in the presence and absence of a variety of hormonally related risk factors. This population was particularly amenable to the study of the effects of familial factors on breast cancer risk, since a relatively large proportion of the women who volunteered for the program had a family history of breast cancer.

## METHODS

Study subjects were selected from the BCDDP, a multicenter breast cancer-screening program involving over 280,000 women at 29 widely dispersed centers. This program, jointly sponsored by the American Cancer Society and the National Cancer Institute, recruited women between 1973 and 1975 for a 5-year program of annual breast examinations by combined modalities of physical examination, mammography, and thermography. The present investigation used the case–control approach, with cases consisting of participants at 28 of the centers whose breast cancer was detected during the period July 1973 to May 1977. Control subjects were selected from participants who had not received a recommendation for biopsy or a biopsy during the course of the screening. These control subjects were chosen to be comparable to the cases on the following factors: screening center, race (white, black, oriental, other), age (same 5-yr group), time of entry (same 6-mo period), and length of continuation in the program (controls had to have had at least as many years of screening as comparable cases).

Home interviews were conducted by nurse interviewers who had been standardly trained. Completed interviews were obtained from 1,375 controls (74.2% of eligible subjects) and 1,552 cases (86.1%). The lower response rate for controls than for cases was primarily due to the fact that controls had moved and were unavailable for interviews (12.9% controls vs. 5.0% cases unavailable) and to their more frequent refusals to be interviewed (10.5% controls vs. 4.6% cases). In addition, 2.4% of the controls and 4.3% of the cases had died, and interviews were not attempted with proxy respondents. Women who were interviewed, however, did not differ significantly from those not interviewed with regard to a number of factors determined for each woman at entry to the BCDDP—including age, race, family income, and history of surgery for benign breast disease.

The cases were interviewed at various intervals after diagnosis. However, in the analyses, exposure information was truncated at the time of diagnosis for cases or the equivalent period for controls. A number of women (60 cases and 11 controls) reported a history of breast cancer prior to entering the BCDDP and were excluded from the present analysis. We also restricted this analysis to white subjects (who comprised 91% of the entire study population). The final study group consisted of 1,362 cases and 1,250 controls.

The measure of association used for the evaluation of effects of an exposure factor is the RR, as estimated by the

ABBREVIATIONS USED: BCDDP=Breast Cancer Detection Demonstration Project; CI=confidence interval; RR=relative risk(s).

[1] Received December 14, 1981; accepted May 5, 1982.

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odds ratio. Confounding variables were evaluated by stratified techniques, with maximum likelihood estimates of combined ratios and 95% CI derived (*19*). For multiple levels of exposure, significance was assessed with the use of a one-tailed linear trend test (*20*). For assessment of the effects of interactions of variables, factors were cross-tabulated and risks computed in relation to women who did not possess either factor (i.e., the referent group). Interactive effects of factors were further assessed with the use of a disease probability (prospective) logistic model (*21*), which entered family history as an independent factor (exposure variable) and the potential interactive factor as both an independent variable and an interaction term, i.e., as both a confounding variable and an effect modifier. These interactive factors, as well as other potential confounding variables, were considered to contribute significantly to the model if the absolute value of the *T*-statistic was greater than 1.96.

## RESULTS

Risks associated with having various relatives affected with breast cancer are shown in table 1. A history of breast cancer in a first-degree relative (mother, sister, or daughter) was reported by 304 patients (22.4%) as compared to 152 controls (12.2%). This resulted in an RR of 2.1 (95% CI: 1.7–2.6). Of the cases, 170 (12.5%) reported a mother and 159 (11.7%) a sister with breast cancer. The RR associated with having a mother with breast cancer was 2.1 (1.6–2.8), whereas the RR associated with having an affected sister was 2.3 (1.7–3.1). The estimate associated with having an affected sister was not confounded by women with breast cancer having more sisters than those without cancer. A small proportion of cases (2.1%) reported having both a mother and a sister affected, a condition associated with an excessively high risk (5.8; 95% CI: 2.5–13.5).

Information was also collected on history of breast cancer in paternal and maternal grandmothers. A substantial proportion of the subjects were unable to recall such information (21.2% unknown response for question regarding paternal grandmother and 13.2% for maternal grandmother). An unknown response initially appeared to be associated with significantly elevated risks; however, adjustment for history of breast cancer in a first-degree relative abolished this association. Analysis of provided information revealed nonsignificant risks associated with having affected grandmothers. The risks were similar for either ancestral line, with the RR being 1.3 (0.7–2.5) for a positive history in a paternal grandmother and 1.4 (0.9–2.4) in a maternal grandmother.

Information on first-degree relatives was further examined according to age at diagnosis of the study subjects. The highest RR occurred among women whose breast cancer was diagnosed before the age of 40 (table 2). For these women, the RR was 5.3 (1.4–20.5). This excess derived primarily from patients having an affected mother. However, risks were also elevated for younger women who reported a sister with breast cancer.

The relationship of a maternal history of breast cancer was examined further according to age at onset of the mothers' breast cancer and to whether or not the disease was bilateral. Risks were dichotomized according to whether the mothers' disease was detected before or after age 50, an age selected because of its approximate correspondence with the onset of menopause. As seen in table 3, the RR was 1.4 for women whose mothers' disease was diagnosed prior to the age of 50 and 2.1 for women whose mothers' disease had a later onset. However, significantly more cases than controls were unable to provide information on their mothers' age at onset of breast cancer. A similar pattern of risk emerged when data on bilaterality were examined. Women whose

TABLE 1.—*RR associated with history of breast cancer in various first- and second-degree relatives*[a]

| Family history of breast cancer | Cases | Controls | RR[b] | 95% CI |
|---|---|---|---|---|
| None in first-degree relative | 1,054 | 1,094 | 1.00 | — |
| In first-degree relative | 304 | 152 | 2.08 | 1.7–2.6 |
| Mother | 170 | 84 | 2.10 | 1.6–2.8 |
| Sister | 159 | 71 | 2.32 | 1.7–3.1 |
| Mother or sister | 301 | 150 | 2.08 | 1.7–2.6 |
| Mother and sister | 28 | 5 | 5.81 | 2.5–13.5 |
| In paternal grandmother | | | | |
| No | 1,057 | 947 | 1.00 | — |
| Yes | 28 | 19 | 1.30 | 0.7–2.5 |
| Unknown | 273 | 280 | 0.84 | 0.7–1.0 |
| In maternal grandmother | | | | |
| No | 1,126 | 1,059 | 1.00 | — |
| Yes | 48 | 28 | 1.44 | 0.9–2.4 |
| Unknown | 184 | 159 | 1.04 | 0.8–1.3 |

[a] Unknown responses with regard to breast cancer in first-degree relatives were excluded from the analysis.

[b] RR associated with family history in grandmothers were adjusted by family history in a first-degree relative.

TABLE 2.—*RR associated with breast cancer in a first-degree relative by age at diagnosis of study subjects*[a]

| Age at diagnosis, yr | Cases | Controls | RR | 95% CI |
|---|---|---|---|---|
| <40 | 11 | 3 | 5.26 | 1.4–20.5 |
| 40–44 | 20 | 11 | 1.87 | 0.8–4.1 |
| 45–49 | 46 | 28 | 1.54 | 0.9–2.6 |
| 50–54 | 70 | 34 | 2.08 | 1.3–3.2 |
| 55–59 | 54 | 25 | 2.23 | 1.3–3.7 |
| ≥60 | 103 | 51 | 2.21 | 1.5–3.2 |
| Total (age-adjusted) | 304 | 152 | 2.08 | 1.7–2.6 |

[a] Unknown responses with regard to breast cancer in first-degree relatives were excluded from the analysis.

TABLE 3.—*RR of breast cancer by characteristics of breast cancer in mother*[a]

| Characteristics of breast cancer in mother | Cases | Controls | RR[b] | 95% CI |
|---|---|---|---|---|
| No history in mother | 1,167 | 1,156 | 1.00 | — |
| Age at diagnosis, yr | | | | |
| <50 | 31 | 22 | 1.39 | 0.8–2.5 |
| ≥50 | 127 | 59 | 2.13 | 1.5–3.0 |
| Unknown | 12 | 3 | 4.01 | 1.0–17.9 |
| Bilaterality | | | | |
| Bilateral | 17 | 19 | 0.88 | 0.4–1.8 |
| Unilateral | 143 | 62 | 2.28 | 1.7–3.2 |
| Unknown | 10 | 3 | 3.29 | 0.8–15.1 |

[a] Unknown responses with regard to breast cancer in the mother were excluded from the analysis.

[b] RR were adjusted by age at diagnosis of study subjects.

mothers' disease was bilateral demonstrated no excess RR (0.9), whereas a significant excess RR (2.3) was associated with unilateral disease in the mother. An unknown response to whether the mother's disease was bilateral or not was also associated with a nonsignificant increase in risk (3.3). These same patterns of risk were seen in relation to characteristics of the mothers' breast cancer when analysis considered age and menopause status of the study subjects.

For assessment of possible confounding effects, correlations of familial occurrence with other breast cancer risk factors were examined among the control subjects (table 4). This analysis demonstrated that women with a family history of breast cancer in a first-degree relative had a different distribution of age at menarche than women without a family history; i.e., women with a family history tended to have either early or late menarche. In addition, those with a family history had a significantly later age at first live birth than those without affected relatives, as well as an earlier age at oophorectomy when this procedure was performed. The variable of age at oophorectomy, however, did not differ significantly between women with and without a family history of breast cancer. Other factors, including age,

TABLE 4.—*Distribution of selected breast cancer risk factors among control subjects by family history of breast cancer in a first-degree relative*[a]

| Characteristics of control subjects | Family history of breast cancer[b] | | No family history of breast cancer[c] | |
|---|---|---|---|---|
| | No. | Percent | No. | Percent |
| Age at menarche, yr | | | | |
| <12 | 27 | 17.9 | 167 | 15.3 |
| 12 | 33 | 21.8 | 259 | 23.8 |
| 13 | 33 | 21.8 | 342 | 31.4 |
| 14 | 30 | 19.9 | 165 | 15.2 |
| ≥15 | 28 | 18.5 | 156 | 14.3 |
| Chi-square test | | $\chi^2_4$=8.22 ($P$=0.08) | | |
| Age at first live birth, yr | | | | |
| Nulliparous | 24 | 15.8 | 169 | 15.4 |
| <20 | 14 | 9.2 | 132 | 12.1 |
| 20–24 | 43 | 28.3 | 419 | 38.3 |
| 25–29 | 51 | 33.6 | 278 | 25.4 |
| ≥30 | 20 | 13.2 | 96 | 8.8 |
| Chi-square test | | $\chi^2_4$=10.65 ($P$=0.03) | | |
| Menopause status | | | | |
| Premenopausal | 41 | 27.3 | 338 | 31.3 |
| Ovaries retained | 85 | 56.7 | 591 | 54.7 |
| Ovaries removed | 24 | 16.0 | 152 | 14.1 |
| Chi-square test | | $\chi^2_2$=1.10 ($P$=0.58) | | |
| Age at menopause–ovaries retained, yr | | | | |
| <45 | 23 | 27.4 | 176 | 30.2 |
| 45–49 | 28 | 33.3 | 173 | 29.7 |
| 50–54 | 26 | 31.0 | 194 | 33.3 |
| ≥55 | 7 | 8.3 | 40 | 6.9 |
| Chi-square test | | $\chi^2_3$=0.87 ($P$=0.83) | | |
| Age at menopause–ovaries removed, yr | | | | |
| <40 | 10 | 41.7 | 45 | 29.6 |
| 40–44 | 5 | 20.8 | 45 | 29.6 |
| 45–49 | 5 | 20.8 | 37 | 24.3 |
| ≥50 | 4 | 16.7 | 25 | 16.4 |
| Chi-square test | | $\chi^2_3$=1.63 ($P$=0.65) | | |

[a] Unknown responses were excluded from the analysis.
[b] Total No.: 152.
[c] Total No.: 1,094.

TABLE 5.—*Breast cancer risk by history of breast cancer in a first degree relative and age at menarche*[a]

| Family history of breast cancer | Age at menarche, yr | Cases | Controls | RR[b] | 95% CI |
|---|---|---|---|---|---|
| No | <12 | 194 | 167 | 1.00 | — |
| | 12 | 255 | 259 | 0.85 | 0.6–1.1 |
| | 13 | 313 | 342 | 0.78 | 0.6–1.0 |
| | ≥14 | 280 | 321 | 0.74 | 0.6–0.9 |
| Yes | <12 | 55 | 27 | 1.76 | 1.1–2.9 |
| | 12 | 73 | 33 | 1.89 | 1.2–3.0 |
| | 13 | 83 | 33 | 2.22 | 1.4–3.5 |
| | ≥14 | 89 | 58 | 1.34 | 0.9–2.0 |

[a] Unknown responses were excluded from the analysis.
[b] RR were adjusted by age at diagnosis of study subjects. $\chi_1$ for linear trend: without family history=−2.23 ($P$=0.01) and with family history=−0.92 ($P$=0.18).

parity, number of miscarriages, menopause status, number of previous breast biopsies, weight, height, oral contraceptive use, menopausal estrogen use, and family income or education, did not differ between women with a family history of breast cancer and those without such a history.

Because of the differences observed, risk estimates associated with having various relatives affected with breast cancer were adjusted for possible confounding effects of age at menarche, age at first live birth, and age at bilateral oophorectomy. Control for these factors did not substantially alter the risk estimates associated with a family history in any first-degree relative. In addition, use of multivariate models with simultaneous control for a number of factors did not alter the previously derived crude estimates associated with a family history of breast cancer or those associated with specific attributes of family history, such as bilaterality and young age at onset of mothers' breast cancer.

Further analysis pursued the effects of a family history in relation to the presence and absence of a variety of breast cancer risk factors.

Effects of varying ages at menarche according to the presence or absence of a family history of breast cancer are shown in table 5. There was a significant decreasing trend ($P$=0.01) in risk with increasing age at menarche among women without a family history. Although the lowest risk occurred in the oldest age at menarche grouping among those with a family history, there was no consistent or significant trend in the RR. In fact, prior to the last grouping, the RR actually increased with increasing ages at menarche.

In contrast to age at menarche, parity and age at first live birth showed similar effects in both the presence and absence of a family history of breast cancer (table 6). In both groups, there was evidence of increasing risk with later ages at first childbirth. For women without a history of breast cancer, the RR increased significantly ($P$<0.01) with increasing age at first birth. Women who delayed their first childbirth until 30 years of age or later showed a 2.7-fold increased risk compared to those who had their first child before the age of 20. Nulliparous women had risks similar to those who had their first childbirth between the ages of 25 and 29. (RR compared to RR of women with a live birth prior to age 20 were 1.8 and 2.0, respectively.) Among women with a family history of breast cancer, those with a birth after the age of 30 were at highest risk, five times (95% CI: 2.8–9.1) that of the referent group (women without a family history of breast cancer and who had their first childbirth prior to the age of 20).

Table 7 shows the RR associated with family history of breast cancer and history of biopsies for benign breast disease. Among those without a family history, risk increased slightly with the number of previous biopsies for benign breast disease. Those who reported two or more biopsies had a risk 1.5 times that of women without any previous biopsies. A similar increasing trend in risk with number of benign breast disease biopsies was seen for those with a family history of breast cancer. As compared to the referent group, those with a family history and no biopsies had a risk of 2.0, those with one biopsy had a risk of 2.3, and those with two or more biopsies had a risk of 5.6.

The examination of risks according to menopause status is presented in table 8. In this analysis, it was necessary to adjust estimates among the menopausal woman by age at menopause and by hormone usage, since these variables acted as negative confounders. Women with a family history of breast cancer who had undergone a bilateral oophorectomy demonstrated an RR of 1.8 compared to nonfamilial subjects with other types of menopause (the referent group).

TABLE 6.—*Breast cancer risk by history of breast cancer in a first-degree relative and age at first live birth*[a]

| Family history of breast cancer | Age at first live birth, yr | Cases | Controls | RR[b] | 95% CI |
|---|---|---|---|---|---|
| No | <20 | 78 | 132 | 1.00 | — |
| | 20–24 | 337 | 419 | 1.34 | 0.9–1.8 |
| | 25–29 | 320 | 278 | 1.96 | 1.4–2.7 |
| | ≥30 | 151 | 96 | 2.68 | 1.8–3.9 |
| | Nulliparous | 166 | 169 | 1.77 | 1.2–2.6 |
| Yes | <20 | 20 | 14 | 2.41 | 1.2–5.0 |
| | 20–24 | 99 | 43 | 3.79 | 2.4–5.9 |
| | 25–29 | 78 | 51 | 2.65 | 1.7–4.2 |
| | ≥30 | 54 | 20 | 5.04 | 2.8–9.1 |
| | Nulliparous | 51 | 24 | 3.82 | 2.1–6.8 |

[a] Unknown responses were excluded from the analysis.
[b] RR were adjusted by age at diagnosis of study subjects. $\chi_1$ for linear trend: Without family history=6.13 ($P$<0.01) (nulliparas excluded) and with family history=0.62 ($P$=0.27).

TABLE 7.—*Breast cancer risk by history of breast cancer in a first-degree relative and number of previous biopsies for benign breast disease*[a]

| Family history of breast cancer | Previous biopsies for benign breast disease | Cases | Controls | RR[b] | 95% CI |
|---|---|---|---|---|---|
| No | None | 815 | 887 | 1.00 | — |
| | 1 | 159 | 149 | 1.16 | 0.9–1.5 |
| | ≥2 | 80 | 58 | 1.49 | 1.0–2.1 |
| Yes | None | 230 | 126 | 1.98 | 1.6–2.5 |
| | 1 | 43 | 20 | 2.32 | 1.4–3.9 |
| | ≥2 | 31 | 6 | 5.63 | 2.6–12.3 |

[a] Unknown responses were excluded from the analysis.
[b] RR were adjusted by age at diagnosis of study subjects. $\chi_1$ for linear trend: Without family history=2.42 ($P$=0.01) and with family history=2.04 ($P$=0.02).

TABLE 8.—*Breast cancer risk by history of breast cancer in a first-degree relative and menopause status*[a]

| Family history of breast cancer | Menopause status | Cases | Controls | RR[b] | 95% CI |
|---|---|---|---|---|---|
| No | Ovaries retained | 539 | 583 | 1.00 | — |
| | Ovaries removed | 115 | 152 | 0.81 | 0.6–1.1 |
| | Premenopausal | 371 | 338 | 1.30 | 0.9–1.7 |
| Yes | Ovaries retained | 165 | 84 | 2.15 | 1.6–2.8 |
| | Ovaries removed | 43 | 24 | 1.90 | 1.1–3.2 |
| | Premenopausal | 87 | 41 | 2.62 | 1.7–4.0 |

[a] Unknown responses were excluded from the analysis.
[b] RR for premenopausal women were adjusted by age at diagnosis of study subjects; RR for menopausal women were adjusted by age at menopause and menopausal hormone usage.

Risks among those with a family history were similar to those among the other menopause groups, with the RR being 2.6 for premenopausal subjects and 2.2 for those who retained their ovaries during surgical menopause. Women who had a bilateral oophorectomy but no family history of breast cancer were at a slightly lower risk (0.8) than those with other types of menopause.

Logistic analyses were also conducted to examine interactive effects of family history with other breast cancer risk factors. These analyses, which controlled for the influence of confounding variables on interactive effects, showed findings in close concordance with stratified analyses, i.e., no clear interaction with age at first live birth or menopause status, but an interaction of family history with multiple previous benign breast disease biopsies (RR=4.0). In addition, differential effects of age at menarche were seen according to the presence or absence of a family history of breast cancer.

## DISCUSSION

In this study, we found that women who reported to have either a mother or a sister with breast cancer experienced approximately a twofold excess risk of breast cancer, an estimate that agrees with estimates given in previous reports (*2, 10–13*). Our estimates are somewhat lower than those previously derived in a study of BCDDP participants (*22*), possibly as a result of different data collection techniques (mailed questionnaire in previous study vs. home interview in this study). In the present investigation, women who reported both a mother and a sister with breast cancer had an especially high risk, and the effects of family history were greatest for women under age 40 at diagnosis. These findings are also consistent with previous observations (*9, 10, 13*). Women whose mothers had bilateral disease and/or disease at premenopausal ages were not at high risk, a finding for which we have no ready explanation. Our findings may be influenced by the higher proportion of cases than controls who were unable to provide information on the bilaterality of their mothers' breast cancer or on the age of their mothers at diagnosis.

The analysis of interactions between family history of breast cancer and other breast cancer risk factors seemed to be a useful approach toward the understanding of the mechanisms of breast carcinogenesis, since those factors that modify the effects of family history may act through common pathways. Also, since family history is likely to reflect genetic determinants, whereas other factors arise at different times in a woman's life, there was a potential for discernment of periods when familial effects tend to operate.

We observed no modification of the effects of parity, age at first live birth, or age at oophorectomy according to the presence of a family history of breast cancer. For all of these factors, effects among women with a family history were those that would have been predicted on a basis of additivity of RR; i.e., there was no evidence of any multiplicative effects or synergy. For example, additivity would have predicted that women with bilateral oophorectomy and a family history of breast cancer would exhibit a risk approximately 96% greater than that of other menopausal women without a family history; in fact, we actually observed a 90% elevation in risk. However, the effect of age at menarche seemed to be modified by a family history of breast cancer. Among women without a family history, we observed a significant linear trend of decreasing risk with increasing age at menarche, a result consistent with the pattern generally seen in studies that have examined menarche effects without reference to family history (*14*, *23*). This effect, however, was not observed in the presence of a family history. Although this difference could be due to chance, we think it may reflect some biologic interaction, since there was some evidence that risk actually rose with increasing age at menarche up to age 14.

Taken together, our findings suggest that the familial predisposition to breast cancer exerts an influence early in a woman's life. This speculation is based on the observation that familial effects were not modified by age at first live birth or oophorectomy but were modified by age at menarche. In addition, we believe that the effect is probably mediated through a hormonal mechanism, rather than a structural defect in breast tissue. This impression is supported by the observation that control subjects with a family history of breast cancer tended to have early or late menarche, a late first childbirth and a young age at oophorectomy compared to controls without such a family history.

Laboratory studies of high-risk women support the notion that familial predisposition may be mediated through hormonal mechanisms in early reproductive life. Alterations of hormonal profiles have been described among daughters (*24-26*) and among younger rather than older sisters (*27*) of women with breast cancer. This idea is also consistent with the view that breast cancer risk factors can operate at different periods in women's lives (*14*)—in this case, early in reproductive life rather than later in life.

Of special interest was the interaction observed between a history of surgery for benign breast disease and familial occurrence of breast cancer. Among women with and without a family history of breast cancer, a history of only one biopsy was a weak risk indicator; this is consistent with a previous study of BCDDP participants and may reflect the self-selection of women into this screening program (*22*). Women with two or more biopsies, however, were at excess risk: Those without a family history exhibited a 1.5-fold excess risk, whereas those with a family history had a risk of 5.6. The RR of 5.6 is greater than the product achieved by the multiplication of the RR of the individual risk factors: family history in the absence of breast surgery (2.0) and multiple biopsies in the absence of family history (1.5). This synergy seems to imply a common mechanistic pathway of carcinogenesis involved with a family history of breast cancer and with multiple surgeries for benign breast disease.

Thus we conclude that the familial excess of breast cancer is established by early adolescence and is uninfluenced by protective factors introduced later. In addition, although more speculative, the evidence also seems to imply that these familial effects are mediated through a hormonal mechanism. Although there is previous support for this hypothesis, further studies are needed that specifically address the issue. Further assessment and elucidation of mechanisms are also needed for the synergy that we observed between a family history of breast cancer and the occurrence of multiple benign breast disease biopsies.

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